EPA's Perspectives on Hazard Assessment, Risk Assessment, and Data Needs

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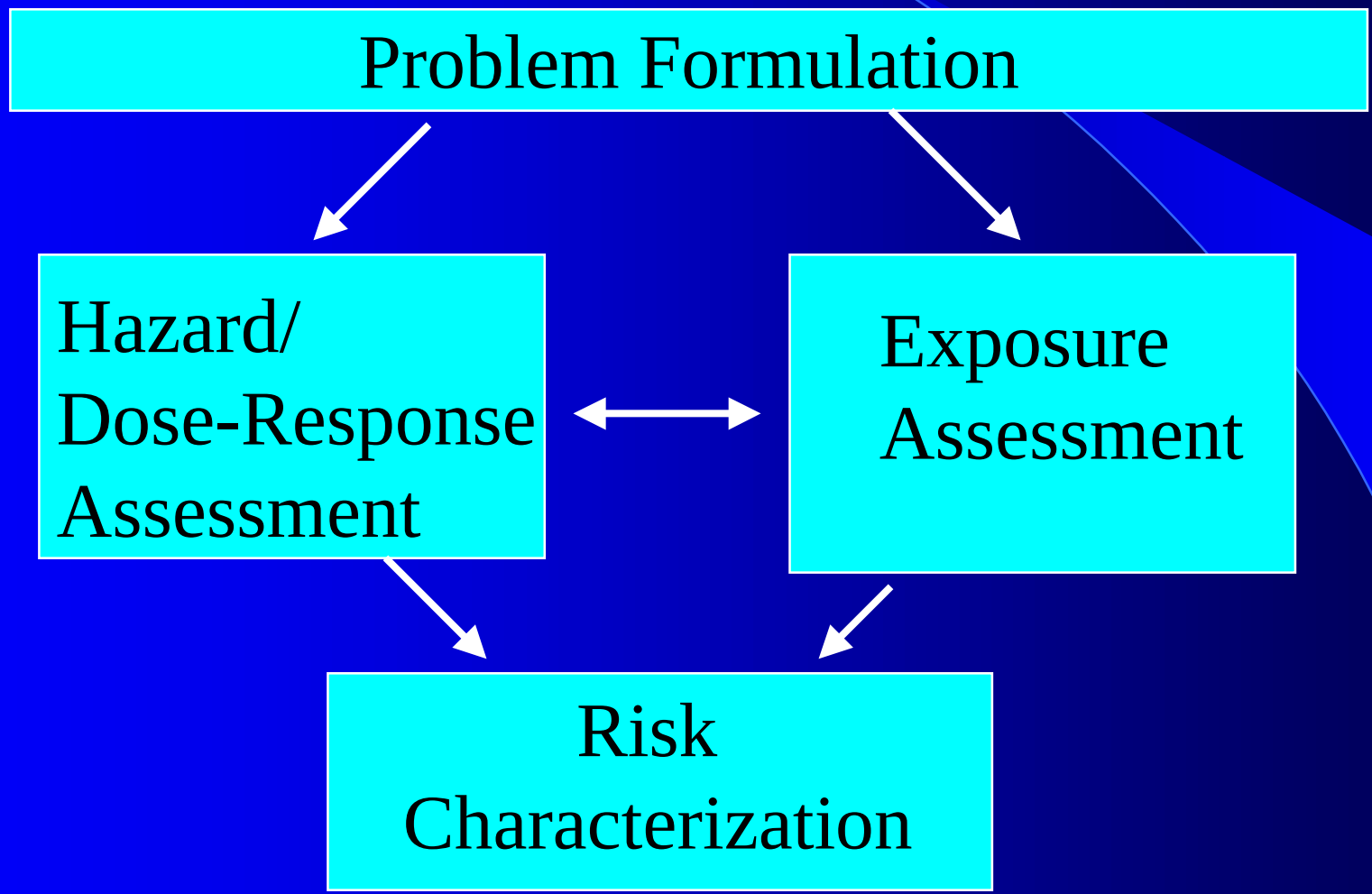
Risk Assessment Paradigm



Problem Formulation

- **Have the potential hazards, exposures and risks to children been adequately characterized?**

Hazard Assessment

- Data may be available from a wide variety of sources including studies conducted according to EPA or OECD guidelines, academic studies, epidemiology studies, case reports, clinical studies
- Evaluate quality and adequacy of each study and the database as a whole

Hazard Assessment - General Guidance

- EPA Test Guidelines
  (http://www.epa.gov/OPPTS_Harmonized)
- EPA Risk Assessment Guidelines
  (http://cfpub.epa.gov/ncea/cfm/nceapubtopics.cfm?ActType=PublicationTopics#r_form)
- HPV Challenge Program
  (http://www.epa.gov/chemrtk)

Hazard Assessment – Adequacy of Studies

- Is there sufficient description of the protocol, statistical analyses, and results to make an evaluation?
- Was an appropriate animal species used? Appropriate sample size? Age? Both sexes?
- Were the dose levels appropriate?
- Were appropriate endpoints assessed?
- Was the duration of exposure adequate?

Hazard Assessment – Adequacy of Studies

- Was an appropriate route of exposure employed?
- Did the study establish dose-response relationships? Was a LOAEL, NOAEL, or BMDL established?
- Are the results biologically plausible?
- Do effects fit with what is known about mode of action?

Characterization of the Database

- Weight of evidence review of studies and database for:
  - consistency of effect, dose-effect relationship, temporal relationship, mode of action, pharmacokinetics
- Extent of the database:
  - use of a narrative description to describe extent, quality, strengths, and limitations of the database

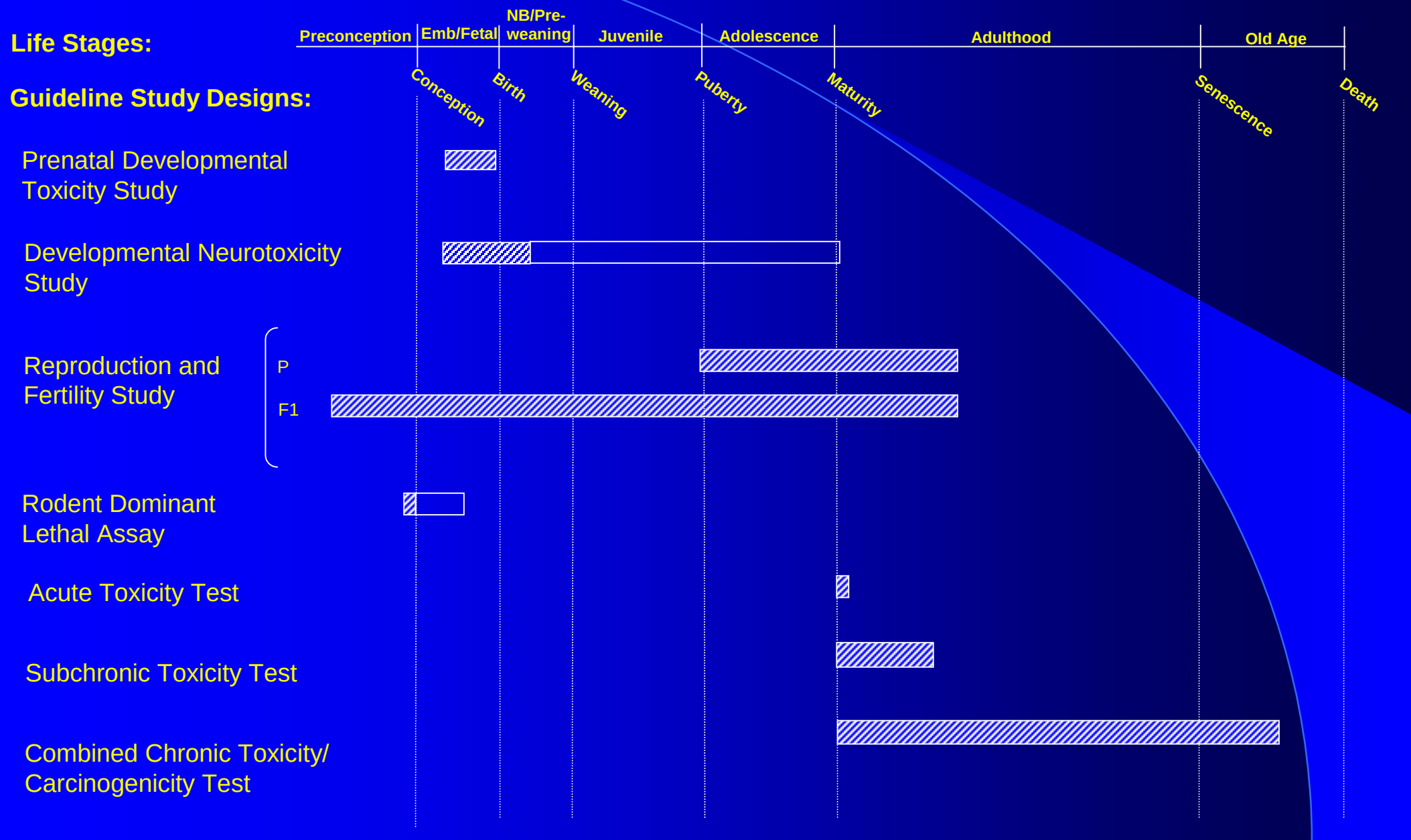
Characterization of the Database

- How well is the toxicity characterized?
- Have adequate studies been conducted to establish the target organs/endpoints?
- Have the effects been characterized for relevant life stages?
- Are the responses consistent across species? Across laboratories?

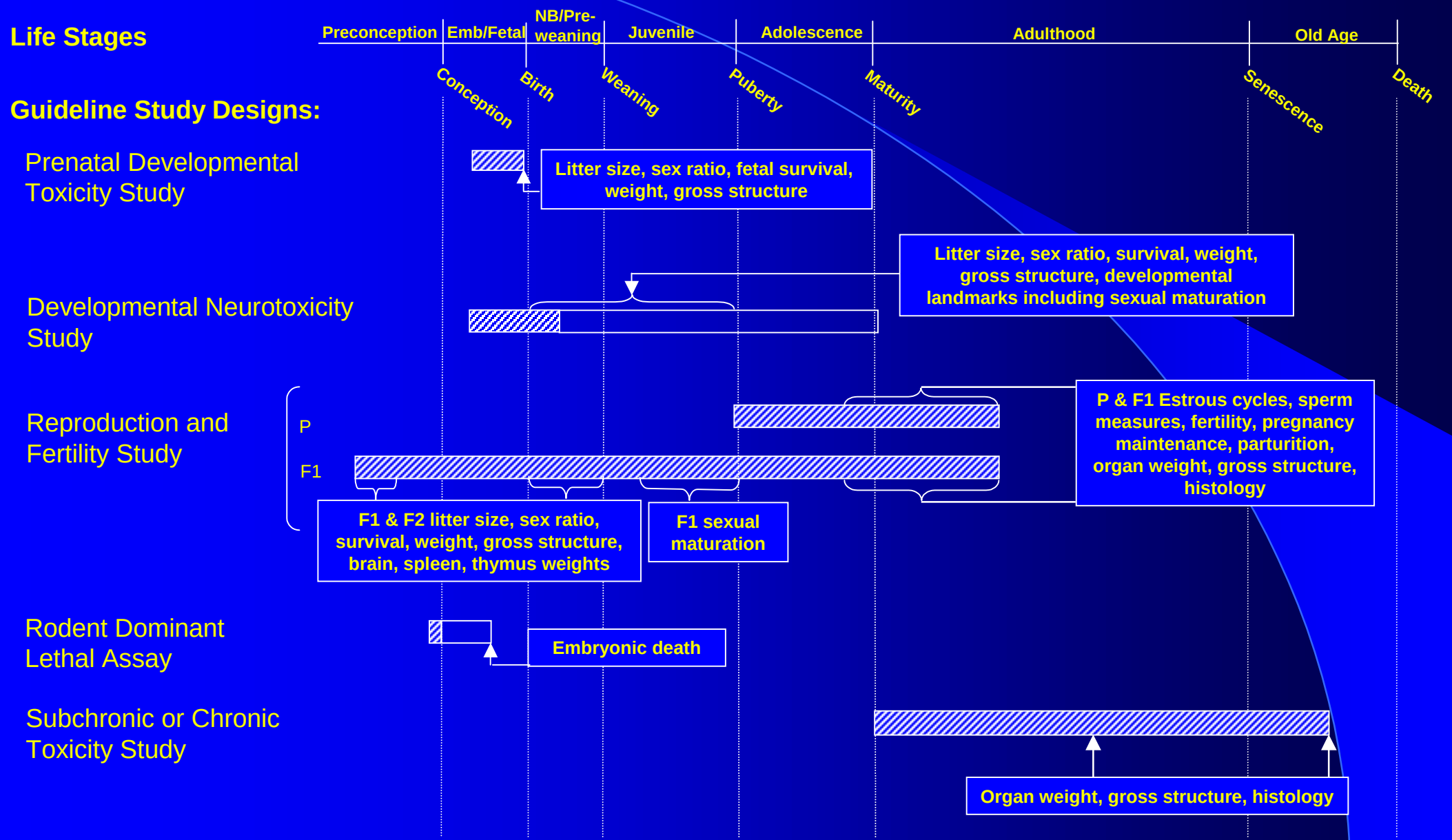
Characterization of the Database

- Are the routes of exposure relevant? Duration of exposure?
- Are the animal species/strains appropriate?
- Are pharmacokinetic data available? If so, are the pharmacokinetics in the animal species similar to humans? Is shape of dose-response curve consistent with pharmacokinetics?

A Life Stage View of Timing and Duration of Exposure in Standard Toxicity Testing Protocols



Reproductive Toxicity Endpoints in Standard Toxicity Testing Protocols



EPA Risk Assessment Forum – Review of the RfD/RfC Process

- Evaluate the current state-of-the-art for hazard and dose-response assessment with a focus on protection of potentially sensitive subpopulations
- Summarize what additional scientific issues can bring to the process
- Raise issues that should be further explored or developed for consideration in the process
- Recognize that the process should not be static, but continually evolving with new information incorporated as new RfDs/RfCs are set, or as they are re-evaluated

Traditional Approach

- Chronic RfD/RfC
- Some program offices also set acute or short-term values
- Focus on a “critical effect/study”
- RfD/RfC = $\frac{\text{NOAEL (LOAEL, BMD)}}{\text{Uncertainty Factors}}$

Setting Acute, Short-term, and Longer-term Reference Values

- Recommended setting acute, short-term, and longer-term reference values, include on IRIS
- Definitions:
  - Acute - $\leq$24 hrs
  - Short-term - >24 hrs - 30 days
  - Longer-term - >30 days - ~ 10% of lifespan
  - Chronic - > ~10% of lifespan

Exposure-Response Array

- Selection of endpoints to use as the POD
  - Use a visual display data to depict all relevant endpoints for various routes and durations of exposure
  - Allows modeling of multiple dose-response curves and dosimetric adjustment of BMDLs to derive HECs and HEDs
  - Allows consideration of all data in the selection of appropriate endpoints for different route and duration reference values
  - Multiple endpoints may be used as the basis for the POD

Risk Characterization

- General guidance:

  EPA Risk Characterization Handbook
  http://www.epa.gov/ORD/spc/rcmenu.htm
- Principles of TCCR
  - Transparency
  - Clarity
  - Consistency
  - Reasonableness

Risk Characterization – Transparency

- Assessment approach used
- Use of assumptions and their impact on the assessment
- Use of extrapolations and their impact on the assessment
- Use of models vs measurements and their impact on assessment
- Plausible alternatives

Risk Characterization – Transparency

- Impact of one choice versus another on the assessment
- Data gaps and their implications for the assessment
- Uncertainties and their impact on the assessment
- Major risk conclusions and the assessor's confidence and uncertainties in them

Data Needs

- Relate back to problem formulation
- Have the potential hazards, exposures and risks to children been adequately characterized?
- Naturally follow from risk characterization
- What are the uncertainties and what (if any) data would reduce the uncertainties?